53. (new) The pharmaceutical composition of claim 40, wherein the phospholipids are in a liquid crystalline phase at 37°C.

54. (new) The pharmaceutical composition of claim 40, wherein the liposomes are obtainable by extruding phospholipid which is in a liquid crystalline phase at 37°C through polycarbonate filters having a pore diameter of 0.1 micron.

REMARKS

Claims 1-22 have been canceled without prejudice. Applicants specifically reserve the right to prosecute any unclaimed subject matter in related applications. Claims 23-54 have been added. The new claims are fully supported by the specification and do not constitute new subject matter as defined in 35 U.S.C. § 132. Specifically, claims 23 and 40 are supported by the specification at page 1, lines 9-11; page 6, lines 23-25; page 8, lines 21-24; page 9, lines 24 to page 10, line 4; page 11, lines 6-14; page 14, lines 13-19; page 17, lines 2-8; page 17, line 20; and original claim 1. Claim 24 is supported by the specification at page 6, lines 6-10 and claim 25 is supported by the specification at page 28, line 8. Claims 26-32 and claims 41-47 are supported by the specification at page 11, lines 15-37. Claims 33 and 48 are supported by the specification at page 7, lines 32-36. Claims 34-35 and claims 49-50 are supported by the specification at page 10, lines 12-33. Claims 36-39 and 51-54 are supported by the specification at page 9, line 6 to page 10, line 4; page 11, lines 6-14; and page 16, line 37 to page 17, line 23. A copy of the claims that will be pending upon entry of the instant amendment is attached hereto as Exhibit A.

The Applicants respectfully request that the cancellation of claims 1-22 and the addition of new claims 23-54 made herein be entered into the file of the above-identified application and that the remarks herein be fully considered.

1. The Rejection Under 35 U.S.C. §112 First Paragraph, Should Be Withdrawn

Claims 1-3, 7-9, and 13-20 are rejected under 35 U.S.C. §112, first paragraph, because the specification does not provide enablement for generic liposomes in contrast to liposomes made of phospholipids. First, the Applicants invite the Examiner's attention to page 10, lines 33 to page 11, line 5, which states that non-phosphorus containing lipids may

also be used in the present invention. Second, the new claims include liposomes made of phospholipids to more particularly point out and distinctly claim specific subject matter of the invention, thus rendering this rejection moot.

According to the Examiner, the specification also lacks adequate support for the broadly used term "apoproteins" in claim 2. In response, the Applicants invite the Examiner's attention to page 12, lines 11-29 of the specification which discloses that binding to "apoproteins" is particularly useful (such as apoprotein A_1, apoprotein A_2, and apoprotein E); thus providing adequate support for the term "apoprotein" in the new claims. Accordingly, the rejection under 35 U.S.C. §112, second paragraph should be withdrawn.

2. The Rejection Under 35 U.S.C. §112 Second Paragraph, Should Be Withdrawn

Claims 1-22 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. According to the Examiner, claim 1 recites a composition "consisting essentially of" but then requires that the "liposomes are not bound to a drug." Therefore, it is unclear whether the Applicant's intent is to convey that the liposomes contain a drug in the interior and if that is the intent then claim 1 should recite this requirement. In response, the Applicants have deleted the term "liposomes are not bound to a drug" thereby rendering the rejection moot. Accordingly, the rejection under 35 U.S.C. §112, first paragraph should be withdrawn.

3. Rejection Under Obviousness-Type Double Patenting

The Examiner has rejected claims 1-7 and claims 8-22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,139,871 and claims 1-28 of U.S. Patent No. 6,312,719, respectively. Applicants note that claims 1-22 have been canceled thereby rendering the rejection moot with respect to those claims. With respect to new claims 23-54, the Applicants respectfully traverse this rejection in view of the differences between the new claims and claims 1-6 of U.S. Patent No. 6,139,871 as well as claims 1-28 of U.S. Patent No. 6,312,719. In the alternative, the Applicants respectfully request that the Examiner hold this rejection in abeyance until claims 23-54 are otherwise deemed allowable at which time the Applicants may file a terminal disclaimer if appropriate based on the final version of the claims allowed.

4. The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1, 3, and 7 are rejected under 35 U.S.C. § 102(b) as being anticipated by Liu and claims 1, 3-13, 18 and 21-22 are rejected under 35 U.S.C. § 102(b) as being anticipated by EP 0470437 (Hager). According to the Examiner, Liu discloses liposomes of the instant sizes and Hager teaches unilamellar liposomes having an average diameter of 100 nm containing phosphatidylcholine for the treatment of atherosclerosis.

A. Hager Requires Liposomes Significantly Smaller Than 100 nm

In contrast to the Examiner's assertion, Hager does not disclose liposomes having an average diameter of 100 nm. Hager discloses liposomes having a mean particle diameter of between 50 nm and 180 nm, between 70 nm and 130 nm, and less than 100 nm. In all embodiments, Hager teaches that at least some of the liposomes in the distribution range will be significantly less than 100 nm in diameter. In contrast, the liposomes of the presently claimed invention have an average diameter of greater than about 100 nm.[1] Therefore, Hager does not anticipate the claims under 35 U.S.C. § 102(b).

B. Liu Requires Liposomes Composed of 20% Dipalmitoylsuccinylglycerol (a Non-Phospholipid)

Liu discloses acid-sensitive and plasma stable liposomes for drug delivery. The liposomes in Liu are made of dioleoyl-phosphatidylethanolamine and dipalmitoylsuccinylglycerol in a 4:1 ratio with differing amounts of ganglioside GM_1. Neither dipalmitoylsuccinylglycerol or ganglioside GM_1 are phospholipids. However, the claims of the present invention require that the liposomes consist essentially of phospholipids. Therefore, because the liposomes in Liu must consist of at least 20% non-phospholipid (dipalmitoylsuccinylglycerol) and some percentage of ganglioside GM_1 (e.g. 6.25%), the liposomes do not consist essentially of phoshpolipids as required by the claims. Moreover, the liposomes disclosed in Liu are designed to deliver drugs to the cytoplasm of target cells. However, the claims of the present invention are not designed for drug delivery. Accordingly, Liu does not anticipate the claims under 35 U.S.C. § 102(b).

---

[1] Liposome size is critical to the claimed invention because liposomes larger than 100 nm are more efficient (per mg of administered phospholipid) in mobilizing unesterified cholesterol and do not substantially raise esterified cholesterol levels in contrast to smaller liposomes. *See* page 10, *infra*.

5. The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hager above by itself or in view of Williams 1984 and over Williams (1984 or 1986) in view of Liu. Claims 5 and 11 are further rejected under 35 U.S.C. § 103(a) as being unpatentable over Hager by itself or in view of Williams 1984 and Barenholz (4,812,314); and over Williams (1984 or 1986) in view of Liu and Barenholz.

A. Claims 1-22 are not obvious over Hager above by itself or in view of Williams 1984

According to the Examiner, Hager does not provide specific examples for the treatment of atherosclerosis, nor that phosphatidylcholine may be derived from eggs, nor the protocol and mode of administration. Thus, in the absence of a showing of unexpected results, such parameters are deemed obvious because they may be manipulated by the artisan to obtain the best possible results. According to the Examiner, one of ordinary skill in the art would be motivated to administer the liposomes of Hager by an intravenous injection, with the expectation of obtaining similar results since the reference of Williams 1984 teaches the administration of similar liposomes for the treatment of the same disease (Willaims, pages 417-18, 422, 424-25 in particular). The Applicants respectfully traverse the Examiner's conclusions.

First, as stated above Hager discloses liposomes having a mean particle diameter of between 50 nm and 180 nm, between 70 nm and 130 nm, and less than 100 nm. In all embodiments, Hager teaches that at least some of the liposomes within each distribution range disclosed will be significantly less than 100 nm in diameter. Likewise, Williams 1984 only discloses unilamellar liposomes having diameters of between 21-50 nm (page 419, lines 22-23) and 30-60 nm (page 422, lines 43-45). In contrast, the liposomes of the presently claimed invention have an average diameter of greater than about 100 nm.

This is important because prior to the present invention, small liposomes (*e.g.*, 21-60 nm) were thought to be advantageous over larger ones. For example, it was generally assumed that the smaller the liposome size, the greater the circulation half-life, and therefore the more cholesterol mobilized. (Gregoriadis and Senior, Life Sci. 113:183-192 (1986)). It was also expected that smaller liposomes would produce a greater number of HDL-like particles, thus promoting efflux of sterol from peripheral tissues (see page 5, lines 22-34 of

the specification citing several prior publications related to this subject). In fact, according to Williams 1984, the specific uptake of liposomes by the liver *in vivo* is slightly enhanced when the liposomes are especially small thus promoting cholesterol efflux and removal from the body (see Williams 1984, page 423, lines 25-27). Accordingly, the view prior to the present invention was that small liposomes (*i.e.*, 21-60 nm) were better than larger ones.

However, small liposomes, such as those disclosed in Williams 1984 and Hager, frequently cause an undesirable elevation in esterified cholesterol levels which is associated with the development and progression of atherosclerosis; thereby destroying the usefulness of the composition for clinical use. *See id.* at 426. In contrast, the present invention is based on the unexpected and surprising discovery that liposomes larger than about 100 nm have the advantages discussed above, are more efficient in mobilizing unesterified cholesterol, and do not substantially raise esterified cholesterol levels (*see* Rodrigueza et al., *Large Versus Small Unilamellar Vesicles Mediate Reverse Cholesterol Transport In Vivo Into Two Distinct Hepatic Metabolic Pools: Implications For the Treatment of Atherosclerosis,* 17 ARTERIOSCLER. THROMB. VASC. BIOL. (10): 2132-39, 2134 (1997) (large unilamellar liposomes (120 nm) were more efficient in mobilizing unesterified cholesterol than small unilamellar liposomes (35 nm), and animals treated with small unilamellar liposomes developed elevated concentrations of esterified cholesterol in contrast to animals treated with the larger liposomes which showed no change in esterified cholesterol). Accordingly, the claims are not obvious over Hager by itself or in view of Williams 1984.

B. Claims 1-22 are not obvious over Williams (1984 or 1986) in view of Liu

According to the Examiner, although Williams 1984 fails to teach the presently claimed liposome size parameters in treating atherosclerosis, such parameters are deemed obvious because they may be manipulated by an artisan to obtain the best possible results. The presently claimed sizes are also deemed to be obvious in view of Liu's teachings that SUVs of about 120 nm have greater circulation time. In addition, Williams 1986 discloses a method of removing serum cholesterol using liposomes without teaching the presently claimed sizes (although it does disclose the use of a 0.22 filter). Thus, according to the Examiner, the liposomes of Williams (1984 or 1986) having sizes within the claimed

range would have been obvious to one of ordinary skill in the art since liposomes with the sizes disclosed by Liu are able to survive the circulation system for longer periods thereby enhancing the removal of cholesterol. The protocol of administration is deemed to be an obvious parameter manipulated by an artisan. The Applicants respectfully traverse the Examiner's rejection.

First, as stated above, the liposomes in Liu are made of dioleoyl-phosphatidylethanolamine and dipalmitoylsuccinylglycerol in a 4:1 ratio where dipalmitoylsuccinylglycerol is not a phospholipid. Liu additionally requires the inclusion of ganglioside GM_1 (a non-phospholipid). Thus, Liu requires at least 20% non-phospholipid in the form of dipalmitoylsuccinylglycerol and also non-phospholipid in the form of ganglioside GM_1 (6.25%). Accordingly, Liu teaches away from the claimed invention since the claims of the present invention require the liposomes to consist essentially of phospholipids.

Second, according to Liu, the longer circulation period is not due to the size of the liposome but rather is a function of ganglioside GM_1 (page 349, 1st col., line 7-23). Liu states that the inclusion of up to 6.25% GM_1 significantly increases the circulation time of liposomes and reduces the reticuloendothelial system (RES) uptake such that the RES/blood ratio of these "stealth" liposomes is 8.5 fold smaller than that of the ordinary liposomes composed of PC and cholesterol. *Id.* However, the superior action of the presently claimed liposomes is based on the fact that they may be cleared by the Kupffer cells that line the sinusoidal openings in the liver (in contrast to directly accessing the hepatocytes which could increase the risk of liposome overload in the liver). Kupffer cells are part of the reticuloendothelial system. Thus, Liu teaches away from the invention since the liposomes of the present invention are designed to be taken up by the reticuloendothelial system via the Kupffer cells.

The combination of Williams (1984 or 1986) and Liu fails to teach the presently claimed invention because Williams (1984 or 1986) fails to disclose unilamellar liposomes greater than 100 nm and the liposomes of Liu consist of over 20% non-phospholipid in contrast to the present invention which requires the liposomes to consist essentially of phospholipids only. Moreover, a skilled artisan combining Williams (1984 or 1986) with Liu (prior to the present invention) would formulate small liposomes composed of over 20% non-phospholipid designed to avoid uptake by the Kupffer cells, which is contrary

to and teaches away from the claimed invention. Similarly, a person of ordinary skill in the art have wound not have been motivated to combine Liu with Williams (1984 or 1986) to arrive at the present invention for the same reasons.

C. Claims 5 and 11 are not obvious over Hager by itself or in view of Williams (1984) in further view of Barenholz (4,812,314), nor obvious over Williams (1984 or 1986) in view of Liu in further view of Barenholz

According to the Examiner, although the primary references do not teach the phospholipids of claims 5 or 11, the use of such phospholipids would have been obvious to one of ordinary skill in the art in view of Barenholz's teachings of the general ability of phospholipids to remove cholesterol through a variety of physiological transfer proteins. An artisan would expect at least a similar removal of cholesterol by other phospholipids. The Applicants respectfully traverse the Examiner's rejections.

The claims are not obvious over Hager by itself or in view of Williams 1984 in further view of Barenholz or obvious over Williams (1984 or 1986) in view of Liu in further view of Barenholz for all of the reasons stated above and because Barenholz fails to teach a unilamellar liposome composition within the presently claimed size range for the treatment of atherosclerosis, hyperlipidemia, or hypoalphalipoproteinemia. Barenholz teaches using a suspension of small unilamellar liposomes composed predominately of egg phosphatidylcholine for treating cellular aging by exchanging the sphingomyelin and cholesterol of biological membranes with the phosphatidylcholine of the liposomes. Thus, Barenholz does not remedy the deficiencies noted above with respect to Hager by itself or in view of Williams 1984 or with respect to Williams (1984 or 1986) in view of Liu.

Moreover, a skilled artisan combining Barenholz, Hager and Williams 1984 would formulate small liposomes for the purpose of treating cellular aging. Likewise, a skilled artisan combining Barenholz, Williams (1984 or 1986) and Liu would formulate small liposomes for the purpose of treating cellular aging wherein the liposomes would be composed of over 20% non-phospholipid designed to avoid uptake by the Kupffer cells. These combinations clearly teach away from the claimed invention.[2]

---

[2] The Applicants also respectfully note that the need to combine 3 or more references in an attempt to arrive at the claimed invention is in of itself indicative of nonobviousness.

In addition, there is no motivation to combine the references. In rejecting claims under 35 U.S.C. § 103(a) for obviousness there must be some motivation or suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. MPEP § 2143. "The mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination." *See* MPEP § 2143.01, under the heading entitled, "Fact That References Can Be Combined Or Modified Is Not Sufficient To Establish *Prima Facie* Obviousness." Nor is the fact that the claimed invention is within the capabilities of one of ordinary skill in the art sufficient to establish *prima facie* obviousness without some *objective reason* to combine the references. *See* MPEP § 2143.01, under heading entitled, "Fact That The Claimed Invention Is Within The Capabilities Of One Of Ordinary Skill In The Art Is Not Sufficient By Itself To Establish *Prima Facie* Obviousness."

Here, the Examiner has failed to provide an objective reason to combine Hager, Williams 1984, and Barenholz or Williams (1984 or 1986), Liu, and Barenholz. The Examiner simply states that because Barenholz teaches the general ability of phospholipids to remove cholesterol through a variety of physiological transfer proteins, an artisan would expect at least a similar removal of cholesterol by other phospholipids. No objective reason to combine the references with each other is provided, nor has the Examiner disclosed where the motivation to combine is found, nor why the motivation to combine is proper when it is the Examiner's duty to do so. *See* MPEP § 2142, third paragraph, under the heading entitled, "Establishing A *Prima Facie* Case of Obviousness" (When the motivation to combine the teachings of the references is not immediately apparent, "*it is the duty of the Examiner to explain why the combination of the teachings is proper*." Applicants respectfully assert that there is no motivation to combine the references for the reasons stated above and because Barenholz teaches the use of small unilamellar liposomes for the treatment of cellular aging. No person of ordinary skill in the art would have been motivated to combine Barenholz, Hager, and/or Williams 1984 or Barenholz, Williams (1984 or 1986), and/or Liu to arrive at the presently claimed invention which is directed to a composition of larger liposomes for the treatment of atherosclerosis, hyperlipidemia, and/or hypoalphalipoproteinemia.

CONCLUSION

Entry of the foregoing remarks and amendments is respectfully requested. No fee is believed to be due with this Amendment other than the fee for the Petition For Extension of Time. However, if any other fee is required, please charge the fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-9090.

Respectfully submitted,

Anthony M. Insogna Reg. No. 35,203
by Brian C. Ramey Reg. No. 40,176

Date: August 20, 2002

Anthony M. Insogna (Reg. No. 35,203)
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosures